

Molecular Test for Fragile X Mental Retardation Syndrome

The UNC Hospitals Molecular Genetics Laboratory offers testing of the *FMR1* gene responsible for Fragile X syndrome of mental retardation. The specific defect is an expansion of CGG trinucleotide repeats leading to inactivation of the gene.

Biology of the Disease: Fragile X Syndrome (FraX) is the most common form of inherited mental retardation with an incidence of approximately 1 in 3600 males and 1 in 4000-6000 females. It is characterized by varying degrees of mental retardation, dysmorphic facial features, behavioral disturbances, developmental delay, autism, and macroorchidism in males. Females tend to be less severely affected. The *FMR-1* gene is localized to the long arm of the X chromosome (Xq27.3). A variable number of trinucleotide repeats, (CGG)_n, is located 5' of the *FMR-1* coding sequence, and the number of these CGG repeats is increased in carriers of FraX and even more so in those affected with the disorder. While normal individuals have 5 to about 44 CGG repeats, carriers of the *FMR-1* "premutation" have about 59-200 repeats, and affected persons with the "full mutation" have more than 200 repeats. Expansion of the CGG sequence to greater than 200 repeats causes aberrant methylation of the CpG sites within the repeat as well as CpG sites within the *FMR-1* promoter. This results in transcriptional silencing of *FMR-1* and manifestations of FraX. Women whose genotype lies in the grey zone from 45 to 58 repeats are unlikely to have a child affected by FraX although variable repeat numbers and disease-causing expansions have sometimes been observed among family members.

Clinical Indications for Testing: Candidates for testing include individuals with unexplained mental retardation, developmental delay, autism, post-pubertal macroorchidism in males, a family history of fragile X syndrome, or the fetus of a carrier mother. Genetic counseling is recommended.

Laboratory Testing for the Fragile X mutation: The preferred sample is ACD or EDTA anticoagulated blood (pale yellow top or lavender top, 7ml) which may be refrigerated up to 48 hours prior to testing. Southern blot analysis is performed using the restriction enzymes *EcoRI* and *EagI* and the StB12.3 probe. PCR across the repeat region is used to distinguish alleles in the high-normal range from those in the low-permutation range. (Full mutation alleles (>200 CGG repeats) are too large to be reliably amplified by PCR.) Results are reported as Fragile X genotype, carrier, borderline, or no evidence of Fragile X genotype.

References:

1. Gene Reviews: <http://www.geneclinics.org>
2. The National Fragile X Foundation: <http://www.fragilex.org>

Questions?

Call the UNC Molecular Genetics Lab at (919) 966-4408 or Dr. Jessica Booker at (919) 966-7894.

E-mail: jbooker@unch.unc.edu

Website: http://labs.unchealthcare.org/directory/molecular_pathology/index.html

